CERTIFICATION OF TRANSLATION

The undersigned, Richard Patner, whose address is 4809 Plummers Point Road Oshkosh, WI 54904, United States of America, declares and states as follows:

I am well acquainted with the English and Japanese languages; I have in the past translated numerous Japanese documents of legal and/or technical content into English.

I have been requested to translate into English the attached Japanese document titled "**WO 02/14272. (Thio)urea derivatives, their production and medicine containing said (thio)urea derivatives".**

To a copy of this Japanese document I therefore attach an English translation and my Certification of Translation.

I hereby certify that the attached English translation of "**WO 02/14272. (Thio)urea derivatives, their production and medicine containing said (thio)urea derivatives**" to the best of my knowledge and ability, is an accurate translation.

And I declare further that all statements made herein of my own knowledge are true, that all statements made on information and belief are believed to be true, and that false statements and the like are punishable by fine and imprisonment, or both, under Section 1001 of Title 18 of the United States Code.

Richard Patner

February 6, 2009
Date

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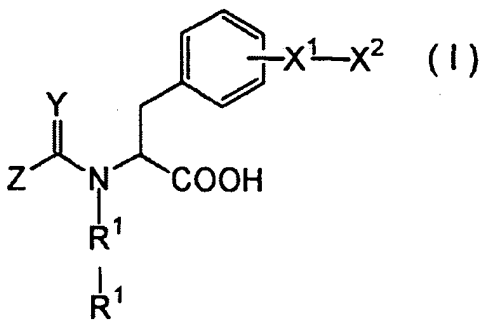
Appended Publications
With international search report

Consult "Guidance notes for codes and abbreviations" cited in the foreword of each PCT gazette that is periodically issued with reference to the two-character codes and other abbreviations.

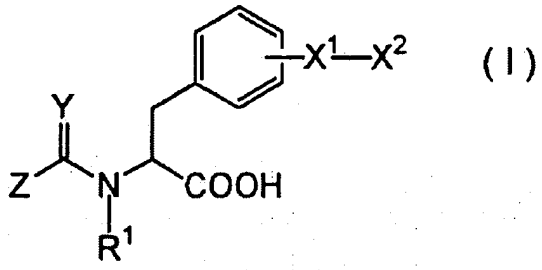
(54) Title: (THIO)UREA DERIVATIVES, PROCESS FOR THEIR PRODUCTION AND MEDICINES CONTAINING THE DERIVATIVES



(I)

(57) Abstract: (Thio)urea derivatives of the general formula (I) or salts thereof; and process for producing the derivatives or the salts: (I) [wherein each symbol is as defined in the description]. The derivatives or the salts are novel compounds exhibiting VLA-4 antagonism, and are useful in medicines as VLA-4 antagonists.

(57) Summary:
(Thio)urea derivatives represented by general formula [I]



(I)

(Each of the notations in the formula is defined in the specifications)
their salts and the method of their production are disclosed.
Aforementioned (thio)urea derivatives and their salts are novel compounds that exhibit VLA-4 antagonism, and they are useful in medicine as VLA-4 antagonists.

Specification

(Thio)urea derivatives, their production and medicine containing said (thio)urea derivatives

Technical Field

The present invention concerns novel (thio)urea derivatives, their production, medicine containing said (thio)urea derivatives, and a method of treatment in which said (thio)urea derivatives are administered. Specifically, the present invention concerns novel (thio)urea derivatives and their salts that exhibit VLA-4 antagonism, an efficient method of their production, medicine containing aforementioned (thio)urea derivatives and their salts as the active ingredient that are useful as VLA-4 antagonists, and a method of treating diseases involving cell adhesion in which aforementioned (thio)urea derivatives or their salts are administered.

Background Technology

Adhesion phenomena are indispensable for complex vital phenomena induced by cellular interaction such as cellular activation, migration, growth, and differentiation. Cell adhesion molecules that are classified by integrin, immunoglobulin, selectin, cadherin, etc., participate in such cell-cell or cell-cell matrix interactions. Integrin, which has an αβ-heterodimer structure, is classified into subfamilies of three principal types of groups, β1, β2, and β3.

β1 integrin is also termed VLA protein. VLA-4 (α4β1) integrin, which is one of them that is expressed in lymphocytes, eosinocytes, basocytes, and monocytes, is a ligand of VCAM-1 and fibronectin. Specifically, VLA-4 plays an important role in the cell-cell interaction or the cell-cell matrix interaction via VCAM-1 and fibronectin.

Leukocytes must infiltrate inflammation sites and become detached by the passage through vascular endothelial cells of leukocytes circulating in blood in order to function in inflammatory tissue.

The binding of VLA-4 and VCAM-1 is one of the most important mechanisms in the strong adhesion of leukocytes and vascular endothelium. Inflammatory cells such as T lymphocytes, B lymphocytes, monocytes and eosinocytes express VLA-4. The VLA-4/VCAM-1 mechanism strongly participates in the infiltration of these cells in inflammatory lesions. Adhesion molecules also play an important role in cell activation via the intercellular interaction. The VLA-4/VCAM-1 mechanism triggers degranulation through eosinocyte activation and the signal via VLA-4 has been clarified to participate in the antigen specific growth activation of lymphocytes.

Inhibition of these inter-molecular bonds via monoclonal antibodies has been attempted to clarify the role of the VLA-4/VCAM-1 mechanism in inflammation. For example, anti-VLA-4 monoclonal antibodies inhibit the adhesion of VLA-4 expressing Ramos cells to human umbilical vein endothelial cells (HUVEC) and to VCAM-1 gene induced COS cells.

Effects of antibodies in numerous animal models are exhibited in both treatment and prevention. For example, significant effects are exhibited in rat adjvant arthritis models (Barbadillo et al., Arthr Rheuma., 1993, 36, 95) as well as contact allergy, delayed allergy models (Ferguson and Kupper, J. Immunol., 1993, 150, 1172; Chisholm et al., Eur. J. Immunol., 1993, 23, 682). In addition, the antibody effect was evaluated in experimental autoimmune encephalomyelitis (Yednock, Nature, 1992, 356, 63), asthma models (Abraham et al., J. Clin. Invest., 1993, 93, 776), and inflammatory bowel disease (IBD) models (Podolsky et al., J. Clin. Invest., 1993, 92, 372).

Furthermore, VLA-4 cell adhesion has been demonstrated to play a role in rheumatoid arthritis, nephritis, diabetes, systemic erythmatosis, delayed allergy, multiple sclerosis, arteriosclerosis, organ transplants and various malignant tumors.

Accordingly, obstruction of VLA-4 by a suitable antagonist would be effective in treating various aforementioned disorders, beginning with inflammation disorders.

Peptide compounds and peptide-like compounds have been presented as VLA-4 antagonists, but all of these have insufficient bioavailability when administered orally, and problems such as *in vivo* degradation persist.

Accordingly, VLA-4 antagonists that have desirable properties for use in treatment and prevention would be desirable.

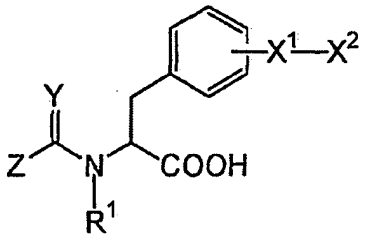
Disclosure of Invention

The first objective of the present invention is to provide a novel compound that exhibits outstanding VLA-4 antagonism in *in vivo* dynamics as well as oral absorption in light of such circumstances. The second objective is to provide an efficient method of producing this compound.

The third objective is to provide medicine that is useful as a VLA-4 antagonist in which aforementioned compound is the active ingredient. A fourth objective is to provide a method of treating disorders involving cell adhesion in which aforementioned compounds are administered.

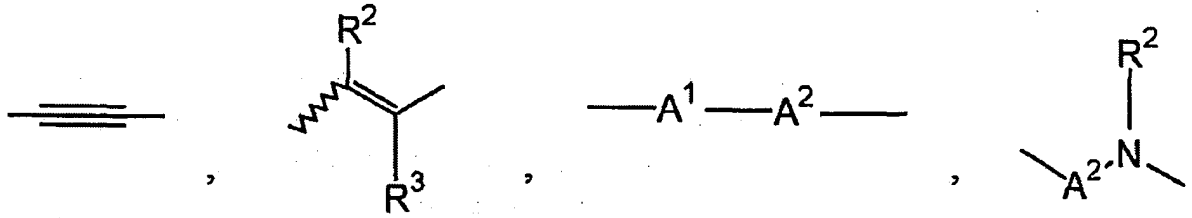
The inventors conducted thorough research to attain aforementioned objectives, the results of which revealed that such compounds as (thio)urea derivatives and their salts having a specific structure and outstanding VLA-4 antagonism could be efficiently produced through specific steps. These findings culminated in the present invention.

Specifically, the first objective of the present invention is attained by (thio)urea derivatives or their salts represented by general formula [I]

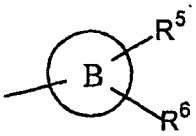


(I)

[In the formula, R^1 represents a hydrogen atom, alkyl group, cycloalkyl group, arylalkyl group or heterocyclic alkyl group, X^1 represents a single bond or the following expression

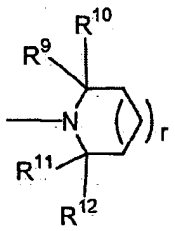


(In the formula, R^2 and R^3 each has the same significance as that of aforementioned R^1, A^1 represents an oxygen atom, sulfur atom, or $-NR^4-$ (In the formula, R^4 has the same significance as R^1), A^2 represents a carbonyl group, thiocarbonyl group, sulfonyl group or $-(CH_2)p-$ (In the formula, p represents an integer of 0 to 5)), X^2 represents the group that is represented by the following expression

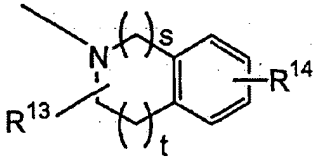


(In the formula, B represents a heterocyclic ring, R^5 and R^6 each independently represent a hydrogen atom, a substituent without an organic group, a hydrocarbon group that is directly bound to the carbon atom of a heterocyclic ring or that is bound via an oxygen atom, sulfur atom, oxycarbonyl group, sulfonyl group or sulfinyl group, $-NR^{15}R^{16}$, $-NR^{15}COR^{16}$ or $-NR^{15}SO_2R^{16}$ (In the formula, R^{15} and R^{16} each independently represents a hydrogen atom, hydrocarbon group, hydrocarbyloxy group, heterocyclic group, or heterocyclic alkyl group.), Y represents an oxygen atom or a sulfur atom, Z represents $-NR^7R^8$ (In the formula, R^7 and R8 each independently represents a hydrogen atom, hydrocarbon group, heterocyclic group, heterocyclic alkyl group, $-CR^{17}R^{18}-(CH_2)q-CONR^{19}R^{20}$, $-CR^{17}R^{18}-(CH_2)q-NR^{19}COR^{20}$, $-CR^{17}R^{18}-(CH_2)q-NR^{19}SO_2R^{20}$, $-CR^{17}R^{18}-(CH_2)1-OR^{19}$, $-CR^{17}R^{18}-(CH_2)q-NR^{19}R^{20}$, $-CR^{17}R^{18}-(CH_2)q-SR^{19}$, $-CR^{17}R^{18}-(CH_2)q-SO_2R^{19}$ or $-CR^{17}R^{18}-(CH_2)q-NR^{19}-V-NR^{20}R^{21}$ (In the formula, R^{17} and R^{18} each

independently represents a hydrogen atom, alkyl group, cycloalkyl group, hydroxyalkyl group, aminoalkyl group, arylalkyl group or heterocyclic alkyl group, R^{19}, R^{20} and R^{21} each independently has the same significance as R^{15}, V represents a carbonyl group or a thiocarbonyl group, q represents an integer of 0 to 5)), the following expression

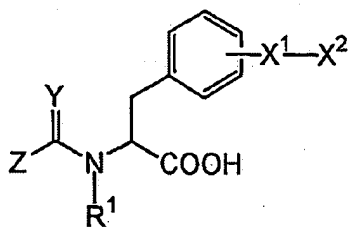


(In the formula, R^9, R^{10}, R^{11}, and R^{12} each independently represents a hydrogen atom, alkyl group having 1 to 6 carbon atoms, r represents an integer of 0 to 3), or the following expression



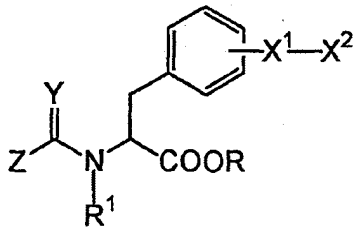
(In the formula, R^{13} and R^{14} each has the same significance as R^1 s and t each independently represents an integer of 0 to 3).]

The second objective is attained by a production method of the (thio)urea derivatives represented by general formula [I]



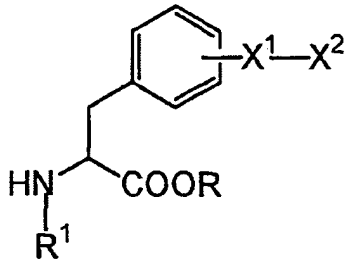
(I)

(In the formula, X^1, X^2, Y, Z and R^1 have the same significance as above)
characterized by hydrolysis of any of the compounds represented by general formula [I-1]



(I-1)

(In the formula, X^1, X^2, Y, Z and R^1 have the same significance as above)
that are derived by reacting the compound represented by general formula [II]



(II)

(In the formula, X^1, X^2, and R^1 have the same significance as above, R represents an alkyl group having 1 to 6 carbon atoms), Z-H (In the formula, Z has the same significance as above), and a carbonyl group- or thiocarbonyl group-inducted reagent.

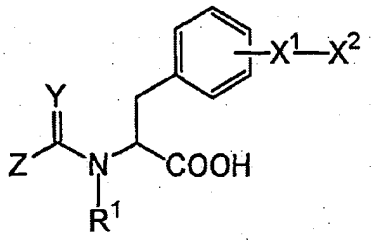
The third objective of the present invention is attained by medicine containing the (thio)urea derivatives represented by aforementioned general formula [I] and their salts as the active ingredient as well as by a VLA-4 antagonist that contains said (thio)urea derivatives and their salts as the active ingredient.

The fourth objective is attained by a method of treating disorders involving cell adhesion in which the (thio)urea derivatives represented by aforementioned general formula [I] and their salts, aforementioned medicine or VLA-4 antagonists are administered.

(Thio)urea derivatives in the present invention connotes both urea derivatives and thiourea derivatives.

Best Mode for Implementing Invention

The (thio)urea derivatives pursuant to the present invention and their salts are compounds represented by general formula [I]

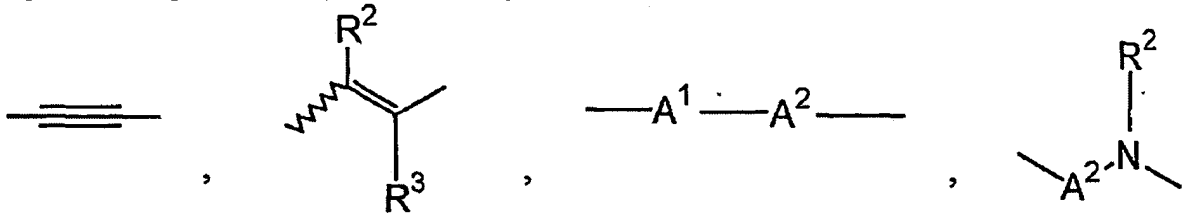


(I)

and their salts.

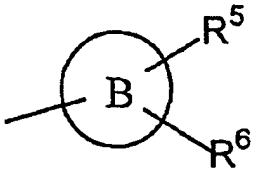
R^1 in aforementioned general formula [I] represents a hydrogen atom, alkyl group, cycloalkyl group, arylalkyl group or heterocyclic alkyl group. Concrete examples include hydrogen atoms, alkyl groups having 1 to 6 carbon atoms, cycloalkyl groups having 3 to 7 carbon atoms, arylalkyl groups having 7 to 13 carbon atoms, heterocyclic alkyl groups having 1 to 6 carbon atoms.

X^1 represents a single bond or any of the following



[In the formula, R^2 and R^3 each independently has the same significance as aforementioned R^1, A^1 represents oxygen atoms, sulfur atoms or $-NR^4-$ (In the formula, R^4 has the same significance as R^1), A^2 represents carbonyl groups, thiocarbonyl groups, sulfonyl groups or $-(CH_2)p-$ (In the formula, p represents an integer of 0 to 5)]

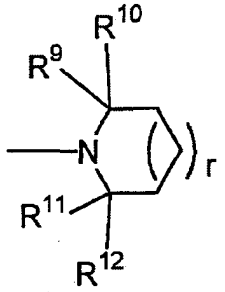
X^2 represents a group represented by the following expression



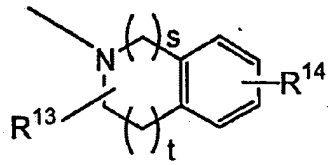
[In the formula, B represents a heterocyclic ring, R^5 and R^6 each independently represent a hydrogen atom, a substituent without an organic group, a hydrocarbon group that is directly bound to the carbon atom of a heterocyclic ring or that is bound via an oxygen atom, sulfur atom, oxycarbonyl group up or sulfinyl group, $-NR^{15}R^{16}$, $-NR^{15}COR^{16}$ or $-NR^{15}SO_2R^{16}$ (In the formula, R^{15} and R^{16} each independently represents a hydrogen atom, hydrocarbon group, hydrocarbyloxy group, heterocyclic group, or heterocyclic alkyl group.). Concrete examples of aforementioned R^5 and R^6 each independently include a hydrogen atom, halogen atom, nitro group, cyano group, hydroxyl group, carboxyl group, alkyl groups having 1 to 6 carbon atoms, cycloalkyl groups having 3 to 7 carbon atoms, alkoxy groups having 1 to 6 carbon atoms, aryl groups having 6 to 10 carbon atoms, arylalkyl groups having 7 to 13 carbon atoms, arylalkoxy groups having 7 to 13 carbon, sulfonyl gro atoms, alkoxycarbonyl groups having 2 to 7 carbon atoms, alkylthio groups having 1 to 4 carbon atoms, alkylsulfonyl groups having 1 to 4 carbon atoms, alkylsulfinyl groups having 1 to 4 carbon atoms, $-NR^{15}R^{16}$, $-NR^{15}COR^{16}$ or $-NR^{15}SO_2R^{16}$ (In the formula, R^{15} and R^{16} each independently represent a hydrogen atom, alkyl group having 1 to 6 carbon atoms, alkoxy group having 1 to 6 carbon atoms, cycloalkyl groups having 3 to 7 carbon atoms, aryl groups having 6 to 10 carbon atoms, arylalkyl groups having 7 to 13 carbon atoms, arylalkoxy groups having 7 to 13 carbon atoms, a heterocyclic ring, or heterocyclic alkyl groups having 1 to 6 carbon atoms.)

Y represents an oxygen atom or sulfur atom.

Z represents $-NR^7R^8$ [R^7 and R^8 each independently represent a hydrogen atom, hydrocarbon group, heterocyclic group, heterocyclic alkyl group, $-CR^{17}R^{18}-(CH_2)q-CONR^{19}R^{20}$, $-CR^{17}R^{18}-(CH_2)q-NR^{19}COR^{20}$, $-CR^{17}R^{18}-CH_2)q-NR^{19}SO_2R^{20}$, $-CR^{17}R^{18}-(CH_2)q-OR^{19}$, $-CR^{17}R^{18}-(CH_2)q-NR^{19}R^{20}$, $-CR^{17}R^{18}-(CH_2)q-SR^{19}$, $-CR^{17}R^{18}-CH_2)q-SO_2R^{19}$ or $-CR^{17}R^{18}-(CH_2)q-NR^{19}-V-NR^{20}R^{21}$ (In the formula, R^{17} and R^{18} each independently represent a hydrogen atom, alkyl group, cycloalkyl group, hydroxyalkyl group, aminoalkyl group, arylalkyl group or heterocyclic alkyl group, R^{19}, R^{20} and R^{21} each independently has the same significance as R^{15}, V represents a carbonyl group or thiocarbonyl group, q represents an integer of 0 to 5)], a group represented by the following formula



(In the formula, R^9, R^{10}, R^{11} and R^{12} each independently represent a hydrogen atom, alkyl group having 1 to 6 carbon atoms, r represents an integer of 0 to 3.) or by the following formula



(In the formula, R^{13} and R^{14} have the same significance as R^1, s and t each independently represent an integer of 0 to 3.). Aforementioned R^7 and R^8 concretely each independently represent a hydrogen atom, alkyl group having 1 to 6 carbon atoms, cycloalkyl group having 3 to 7 carbon atoms, aryl group having 6 to 10 carbon atoms, arylalkyl group having 7 to 13 carbon atoms, heterocyclic group, heterocyclic alkyl group having 1 to 6 carbon atoms, $-CR^{17}R^{18}-(CH_2)q-CONR^{19}R^{20}$, $-CR^{17}R^{18}-(CH_2)q-NR^{19}COR^{20}$, $-CR^{17}R^{18}-(CH_2)q-NR^{19}SO_2R^{20}$, $-CR^{17}R^{18}-(CH_2)q-OR^{19}$, $-CR^{17}R^{18}-(CH_2)q-NR^{19}R^{20}$, $-CR^{17}R^{18}-(CH_2)q-SR^{19}$, $-CR^{17}R^{18}-(CH_2)q-SO_2R^{19}$ or $-CR^{17}R^{18}-(CH_2)q-NR^{19}-V-NR^{20}R^{21}$ (In the formula, R^{17} and R^{18} each independently represent a hydrogen atom, alkyl group having 1 to 6 carbon atoms, a cycloalkyl group having 3 to 7 carbon atoms, a hydroxyalkyl group having 1 to 5 carbon atoms, an aminoalkyl group having 1 to 5 carbon atoms, an arylalkyl group having 7 to 13 carbon atoms and a heterocyclic alkyl group having 1 to 6 carbon atoms, $R^{19}R^{20}$ and R^{21} each independently have the same significance as R^{15}, V represents a carbonyl group or thiocarbonyl group, q represents an integer of 0 to 5).

Each substituent in aforementioned general formula [I] is explained below.

Concrete examples of "halogen atoms" include fluorine atoms, chlorine atoms, bromine atoms, or iodine atoms.

Concrete examples of "alkyl groups having 1 to 6 carbon atoms" include straight-chain or branched-chain alkyl groups such as the methyl group, ethyl group, n-propyl group, isopropyl group, n-butyl group, isobutyl group, tert-butyl group, sec-butyl group, n-pentyl group, tert-amyl group, 3-methylbutyl group, neopentyl group, n-hexyl group.

Concrete examples of "cycloalkyl groups having 3 to 7 carbon atoms" include the cyclopropyl group, cyclobutyl group, cyclopentyl group, cyclohexyl group, and cycloheptyl group.

Concrete examples of "alkoxyl groups having 1 to 6 carbon atoms" include straight-chain or branched-chain alkoxyl groups such as the methoxy group, ethoxy group, n-propoxy group, isopropoxy group, n-butoxy group, isobutoxy group, tert-butoxy group, sec-butoxy group, n-pentyloxy group, tert-amyloxy group, 3-methylbutoxy group, neopentyloxy group, and n-hexyloxy group.

Concrete examples "hydroxyalkyl groups having 1 to 5 carbon atoms" include the hydroxymethyl group, 1-hydroxyethyl group, 2-hydroxyethyl group, and hydroxypropyl group.

Concrete examples of "aminoalkyl groups having 1 to 5 carbon atoms" include the aminomethyl group, 2-aminoethyl group, 3-aminopropyl group, and the 4-aminobutyl group. Furthermore, amino groups may be displaced, and examples of substituents include the methyl group, ethyl group, benzyl group, acetyl group, benzoyl group, methoxycarbonyl group, benzyloxycarbonyl group, and the tert-butoxycarbonyl group.

"Aryl groups having 6 to 10 carbon atoms" would be represented by monocyclic or bicyclic aromatic hydrocarbon groups having 6 to 10 carbon atoms that are unsubstituted or that have 1 to 3 substituents. Concrete examples include the phenyl group, o-tolyl group, 2-methoxyphenyl group, 3-chlorophenyl group, 1-naphthyl group, and the 2-naphthyl group. Examples of substituents include alkyl groups having 1 to 6 carbon atoms, alkoxyl groups having 1 to 6 carbon atoms, halogen atoms, and aryloxy groups having 6 to 10 carbon atoms.

"Arylalkyl groups having 7 to 13 carbon atoms" would be represented by monocyclic or bicyclic aromatic aliphatic hydrocarbon groups having 7 to 13 carbon atoms that are unsubstituted or that have 1 to 3 substituents. Concrete examples include the benzyl group, phenethyl group, 1 (S)-phenylethyl group, 1 (R)-phenylethyl group, 1-phenylpropyl group, 1-naphthylmethyl group, and the 2-naphthylmethyl group. In addition, rings in which aromatic aliphatic hydrocarbon aromatic rings and aliphatic chains are bound may be formed. Concrete examples include indanyl groups and 1,2,3,4-tetrahydronaphthyl groups. Examples of substituents include alkyl groups having 1 to 6 carbon atoms, alkoxyl groups having 1 to 6 carbon atoms, halogen atoms, and aryloxy groups having 6 to 10 carbon atoms.

"Arylalkoxyl groups having 7 to 13 carbon atoms" would be represented by monocyclic or bicyclic aromatic hydrocarbon alkoxyl groups having 7 to 13 carbon atoms that are unsubstituted or that have 1 to 3 substituents. Concrete examples include the benzyloxy group, 1-phenylethoxy group, 2-phenylethoxy group, 1-phenylpropoxy group, 1-naphthylmethoxy group, and 2-naphthylmethoxy group. Concrete examples include alkyl groups having 1 to 6 carbon atoms, alkoxyl groups having 1 to 6 carbon atoms, halogen atoms, and aryloxy groups having 6 to 10 carbon atoms.

"Aryloxy groups having 6 to 10 carbon atoms" would be represented by monocyclic or bicyclic aromatic hydrocarbon oxy groups having 6 to 10 carbon atoms that are unsubstituted or that have 1 to 3 substituents. Concrete examples include the phenoxy group, 2-methylphenoxy group, 4-methoxyphenoxy group, 3,5-dichlorophenoxy group, 1-naphthyloxy group, and the 2-naphthyloxy group. Concrete examples include alkyl groups having 1 to 6 carbon atoms, alkoxyl groups having 1 to 6 carbon atoms, and halogen atoms.

Concrete examples of "alkoxycarbonyl groups having 2 to 7 carbon atoms" include straight-chain or branched-chain alkoxycarbonyl groups such as the methoxycarbonyl group, ethoxycarbonyl group, n-propoxycarbonyl group, isopropoxycarbonyl group, n-butoxycarbonyl group, sec-butoxycarbonyl group, and the tert-butoxycarbonyl group.

Concrete examples of "alkylthio groups having 1 to 4 carbon atoms" include straight-chain or branched-chain alkylthio groups such as the methylthio group, ethylthio group, n-propylthio group, isopropylthio group, n-butylthio group, sec-butylthio group, and the tert-butylthio group.

Concrete examples of "alkylsulfonyl groups having 1 to 4 carbon atoms" would be straight-chain or branched-chain alkylsulfonyl groups such as the methane sulfonyl group, ethane sulfonyl group, n-propylsulfonyl group, isopropylsulfonyl group, n-butylsulfonyl group, sec-butylsulfonyl group, and the tert-butylsulfonyl group.

Concrete examples of "alkylsulfinyl groups having 1 to 4 carbon atoms" would be straight-chain or branched-chain alkylsulfinyl groups such as the methane sulfinyl group, ethane sulfinyl group, n-propylsulfinyl group, isopropylsulfinyl group, n-butylsulfinyl group, sec-butylsulfinyl group, and the tert-butylsulfinyl group.

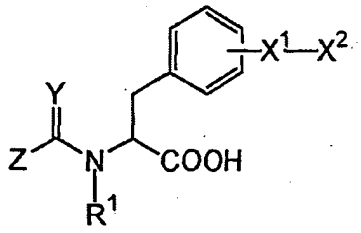
"Heterocyclic groups" would be represented by monocyclic heterocyclic groups having 5 to 7 members that include 1 to 3 heteroatoms selected from among nitrogen atoms, oxygen atoms or sulfur atoms in the ring. Concrete examples include the furyl group, thienyl group, imidazolyl group, thiazolyl group, oxazolyl group, pyridyl group, pyrazinyl group, pyrrolidinyl group, piperidinyl group, piperazinyl group, homopiperazinyl group, morpholinyl group, and the dioxanyl group. In addition, bicyclic or tricyclic condensed heterocyclic groups in which aforementioned monocyclic heterocyclic rings are condensed or in which benzene rings are condensed with aforementioned monocyclic heterocyclic rings would also be represented. Concrete examples include the benzofuranyl group, benzothienyl group, indolyl group, benzimidazolyl group, chromanyl group, piperonyl group, quinolyl group, 1,2,3,4-tetrahydroquinolyl group, and the 5,6,7,8-tetrahydroxypyrido [4,3-d] pyrimidyl group. These may be displaced with examples of substituents such as alkyl groups having 1 to 6 carbon atoms, alkoxyl groups having 1 to 6 carbon atoms, halogen atoms, aryloxy groups having 6 to 10 carbon atoms, hydroxyl groups and amino groups. The same applies to "heterocyclic rings".

"Heterocyclic alkyl groups having 1 to 6 carbon atoms" would represent alkyl groups having 1 to 6 carbon atoms, displaced by aforementioned "heterocyclic groups". Concrete examples include imidazolyl methyl groups, indolyl methyl groups, benzothiazolyl methyl groups, piridyl methyl groups, 1-piridyl ethyl groups, 2-piridyl ethyl groups, 3-thienyl propyl groups, and 2-piperidinoethyl groups.

When asymmetric carbon atoms are present in the compounds pursuant to the present invention represented by general formula [I], their racemates, diasteroisomers and individual optically active forms are also included in the present invention. When geometric isomers are present, (E) forms, (Z) forms and mixtures thereof are also included in the present invention.

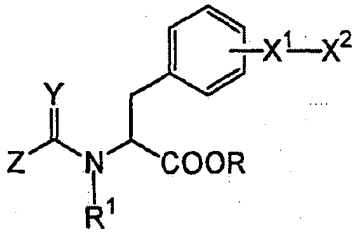
There is no specific limitation on salts of compounds pursuant to the present invention represented by general formula [I] so long as they are pharmacologically permissible salts. Examples include salts of inorganic bases, salts of organic bases, salts of organic acids, salts of inorganic acids, and salts of amino acids. Salts of inorganic bases include alkali metal salts such as sodium salts, potassium salts, calcium salts, as well as ammonium salts. Salts of organic bases include triethylamine salts, pyridine salts, ethanolamine salts, cyclohexylamine salts, and dicyclohexylamine salts. Examples of salts of organic acids include formates, acetates, tartrates, maleates, succinates, and methanesulfonates. Examples of salts with inorganic acids include hydrochlorides, hydrobromides, and nitrates. In addition, examples of salts with amino acids include glycine salts, alanine salts, arginine salts, glutamates, and asparaginates.

The (thio)urea derivatives pursuant to the present invention represented by general formula [I] could be efficiently produced by the method pursuant to the present invention that is presented below. Specifically, in the method pursuant to the present invention, production of the (thio)urea derivatives represented by general formula [I]



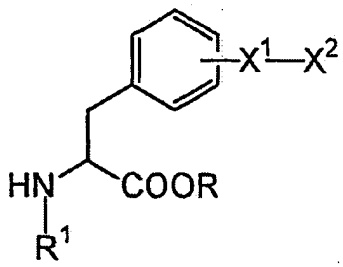
(I)

(In the formula, X^1, X^2, Y, Z and R^1 have the same significance as above)
is characterized by hydrolysis of any of the compounds represented by general formula [I-a]



(I-a)

(In the formula, X^1, X^2, Y, Z, R^1 and R have the same significance as above)
that are derived by reacting the compound represented by general formula [II]

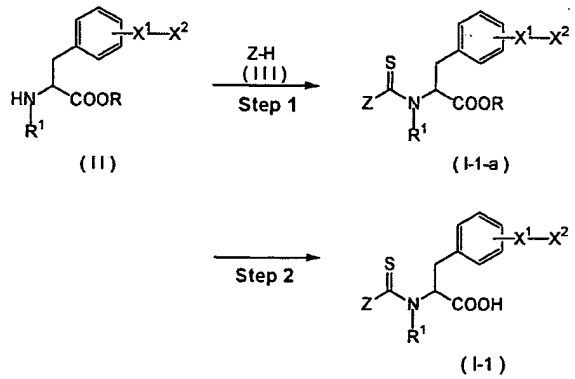


(II)

(In the formula, X^1, X^2, and R^1 have the same significance as above, R represents an alkyl group having 1 to 6 carbon atoms), Z-H (In the formula, Z has the same significance as above), and a carbonyl group- or thiocarbonyl group-inducted reagent.

Concretely, the (thio)urea derivatives pursuant to the present invention can be derived by production methods 1 and 2 below.

[Production method 1]

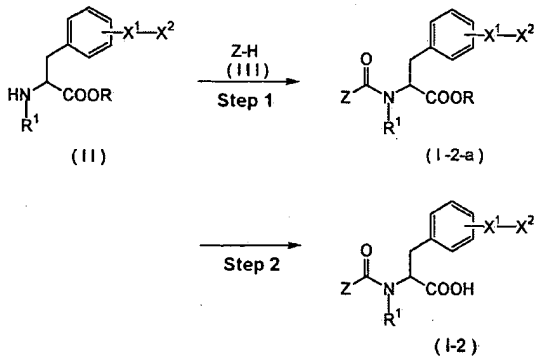


(In the formula, X^1, X^2, R^1, R and Z have the same significance as above.)
Compound (I-1) can be produced by the reactions in step 1 and step 2 below.

(Step 1) In this step, compound (I-1-a) can be produced by reacting compound (II), compound (III) and a reagent in which a thiocarbonyl group has been inducted. Reagents in which a thiocarbonyl group has been inducted include thiocarbonyl diimidazole or thiophosgene. There is no limitation to the reaction solvent so long as it does not markedly interfere with the reaction. Desirable examples include dichloromethane, dichloroethane, and tetrahydrofuran. There is no specific limitation on the reaction temperature, but it would usually be in the range of 0 to 100^{0}C. The reaction time preferably would be in the range of 3 to 72 hours.

(Step 2) Compound (I-1) can be produced in this step by a hydrolysis reaction of compound (I-1-a) derived in step 1 under alkaline conditions. The hydrolysis reaction under alkaline conditions would use known reactions. Examples of alkaline solutions include lithium hydroxide, sodium hydroxide, and potassium hydroxide. There is no specific limitation on the reaction solvent so long as it is an organic solvent that is miscible with water, but methanol, ethanol, tetrahydrofuran, and dimethoxyethane would be preferable. There is no specific limitation on the reaction temperature, but the reaction would preferably be carried out at a temperature range of 0 to 100^{0}C, and the reaction duration would preferably be 30 minutes to 3 hours.

[Production method 2]



(In the formula, X^1, X^2, Y, Z, R^1, and R have the same significance as above.)

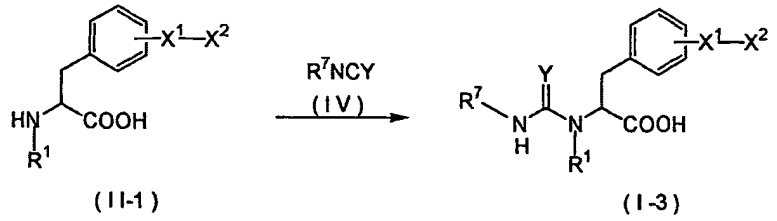
Compound (I-2) can be produced by the reaction in step 1 and step 2 below.

(Step 1) In this step, compound (I-2-a) can be produced by reacting compound (II), compound (III) and a reagent in which a carbonyl group has been inducted. Reagents in which a carbonyl group has been inducted include carbonyl diimidazole, triphosgene and phosgene. This reaction would usually be carried out in the presence of a base. Desirable bases include pyridine, triethylamine, N,N-diisopropylethylamine, and N-methylmorpholine. There is no limitation to the reaction solvent so long as it does not markedly interfere with the reaction. Desirable examples include dichloromethane, dichloroethane, tetrahydrofuran, and dioxane. There is no specific limitation on the reaction temperature, but it would usually be in the range of 0 to 100^{0}C. The reaction time preferably would be in the range of 30 minutes to 24 hours.

(Step 2) In this step, compound (I-2) can be produced by reacting compound (I-2-a) that is derived in step 1 in the same reaction as in step 2 of production method 1.

In addition, the (thio)urea derivative pursuant to the present invention can be produced by production method 3 presented below when Z in general formula [I] is -NHR^7.

[Production method 3]



(In the formula, X^1, X^2, Y, R^1, and R^7 have the same significance as above.)

Compound (I-3) or its salts can be produced by reacting compound (II-1) or its salts with compound (IV). This reaction would usually be carried out in the presence of an inorganic or organic base. Desirable inorganic bases would include sodium hydrogencarbonate, sodium carbonate, potassium carbonate, sodium hydroxide, and potassium hydroxide. Desirable organic bases would include triethylamine, N,N-diisopropylethylamine, 4-methylmorpholine, and pyridine. There is no specific limitation on the reaction solvent so long as it does not markedly interfere with the reaction. The reaction could be carried out in water, methanol, ethanol, isopropyl alcohol, tetrahydrofuran, dioxane, or mixed solvents of these. There is no specific limitation on the reaction temperature, but the reaction would preferably be carried out at a temperature range of 0 to 100^0C, and the reaction duration would preferably be 2 to 10 hours.

The (thio)urea derivatives pursuant to the present invention that are produced by aforementioned method could be isolated and refined as a free-form compound, salts thereof, any of various types of solvates such as hydrates or ethanolates, or as polymorphic crystals. Pharmacological permissible salts of the (thio)urea derivatives pursuant to the present invention could be produced by a conventional salt-production reaction. Isolation-refining could be carried out by suitable chemical procedures, including extraction fractionation, crystallization, and various types of fraction chromatography. Optical isomers could be derived by suitable selection of feedstock compounds or stereochemically pure isomers could be derived by optical resolution of racemic compounds.

The (thio)urea derivatives pursuant to the present invention and their salts exhibit outstanding VLA-4 antagonism. They would be useful as therapeutic or prophylactic medicine for disorders induced by leukocyte adhesion and infiltration or for disorders in which the course of VLA-4 dependent adhesion plays a role. Examples of such disorders include autoimmune diseases such as rheumatoid arthritis, systemic erythmatosis, multiple sclerosis, Sjoegren=s syndrome; various types of visceral inflammations accompanying these disorders; allergic disorders such as asthma, atopic dermatitis, nasal congestion, rhinitis; inflammatory bowel disease containing Crohn=s disease; nephritis, hepatitis, inflammatory disorders of the central nervous system, cardiovascular disorders, arteriosclerosis, diabetes, various malignant tumors, prevention of injury following organ transplant, prevention of tumor growth and metastasis.

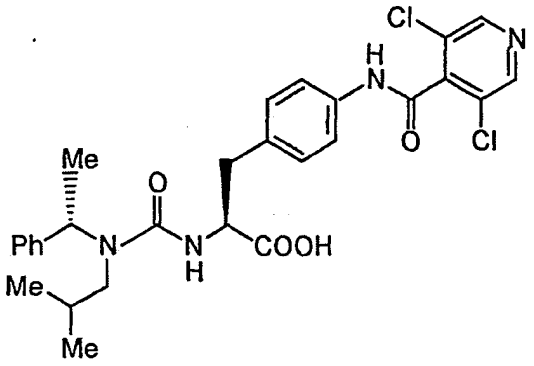
The (thio)urea derivatives pursuant to the present invention and their salts can be administered systemically or locally by such methods as oral administration, intravenous injection, subcutaneous injection, or rectally, but oral administration is the most desirable. The most convenient administration form may be selected as a function of the dosage form or the administration route. Examples include tablets, troches, sublingual tablets, sugar-coated tablets, capsules, pills, powders, granules, liquids, emulsions, syrups, inhalants, eye-drops, nose-drops, injections, and suppositories. Furthermore, these preparations may be produced by incorporating excipients, preservatives, wetting agents, emulsifiers, stabilizers, dissolution adjuvants, etc. The dosage of the (thio)urea derivatives pursuant to the present invention and their salts may be suitably selected based on such conditions as the administration subject, administration route, and symptoms. For example, the dosage of this compound in terms of one dose of the active ingredient when orally administered to a man would usually be in the range of 0.1 to 100 mg/kg, preferably 1 to 30 mg/kg, and administration 1 to 3 times would be preferable.

The present invention is explained in further detail below through working examples, but the present invention is not restricted to these working examples.

The proton nuclear magnetic resonance (^{1}H-NMR) spectrum was measured by JNM-EX270 model spectrometer (270 M Hz, product of Japan Electronic Computer Company (Limited) using tetramethylsilane (TMS) as the internal standard. The δ value is indicated by ppm.

In addition, Me represents a methyl group, Et an ethyl group, Pr a propyl group, Bu a butyl group, and Ph represents a phenyl group in the following structural formulas and tables.

[Working Example 1] 3-[4-[(3,5-dichloropyridine-4-carbonyl)amino]phenyl]-2(S)-[3-isobutyl-3-[1(S)-phenylethyl] ureido] propionate



(Step 1) A dichloromethane solution (2 ml) of 4-[(3,5-dichloropyridine-4-carbonyl) amino]-L-phenylalanine methyl ester (200 mg, 0.54 mmol) and N,N-diisopropylethyl amine (0.12 ml, 0.70 mmol) was added dropwise over 20 minutes to a dichloromethane solution (2 ml) of triphosgene (53 mg, 0.18 mmol) at 0^{0}C. After ten minutes, a dichloromethane solution (2 ml) of N-isobutyl-1 (S)-phenylethyl amine (124 mg, 0.70 mmol) and N,N-diisopropylethyl amine (0.12 ml, 0.70 mmol) was added and stirred for two hours at room temperature. Following the reaction, the solvent was concentrated under vacuum followed by the addition of ethyl acetate to the residue, washing with water, saturated sodium hydrogencarbonate and saturated brine solution, and drying with anhydrous

magnesium sulfate. The solvent was then concentrated under vacuum. The residue was refined via silica gel column chromatography (n-hexane:ethyl acetate volume ratio = 2:1 6 1:1) to yield colorless powder of 3-[4-[(3,5-dichloropyridine-4-carbonyl) amino] phenyl]-2 (S)-[3-isobutyl-3-[1(S)-phenylethyl] ureido] propionic acid methyl ester (223 mg, 72%). The physical values are presented below.

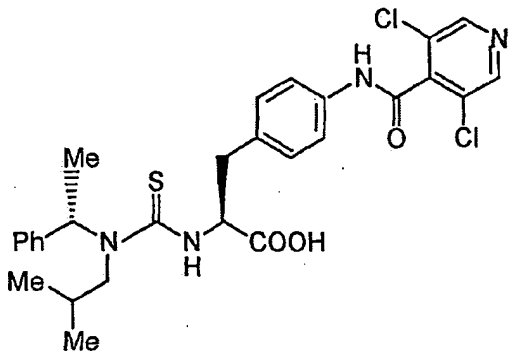
^{1}H-NMR ($CDCl_3$) δ: 8.58 (s, 2H), 7.69 (s, 1H), 7.48 (d, J=8.3 Hz, 2H), 7.37-7.29 (m, 5H), 6.98 (d, J-8.3 Hz, 2H), 5.23 (q, J=7.3 Hz, 1H), 4.86-4.69 (m, 2H), 3.72 (s, 3H), 3.52-2.91 (m, 3H), 2.81 (dd, J=7.3, 14.8 Hz, 1H), 1.79-1.69 (m, 1H), 1.57 (d, J=7.3 Hz, 3H), 0.83 (d, J=6.6 Hz, 3H), 0.76 (d, J=6.6 Hz, 3H).

(Step 2) The 3-[4-[(3,5-dichloropyridine-4-carbonyl) amino] phenyl]-2 (S)-[3-isobutyl-3-[1(S)-phenylethyl] ureido] propionic acid methyl ester (217 mg, 0.38 mmol) was dissolved in methanol (4 ml) and tetrahydrofuran (1 ml), followed by the addition of 2 mol/liter of lithium hydroxide solution (1.34 ml, 2.63 mmol) and stirring for one hour at room temperature. Following the reaction, 2 mol/liter of hydrochloric acid was added at 0^0C to adjust the pH to 3, after which the solvent of concentrated under vacuum. Water was added to the residue, followed by filtration to yield colorless powder of the title compound (206 mg, 97%). The physical values are presented below.

^{1}H-NMR($CDCl_3$)δ: 12.50 (brs, 1H), 10.83 (s, 1H), 8.78 (s, 2H), 7.56 (d, J=8.3 Hz, 2H), 7.32-7.18 (m, 7H), 6.14 (d, J=7.9 Hz, 1H), 5.31 (q, J=6.9 Hz, 1H), 4.45-4.37 (m, 1H), 3.07 (dd, J=5.0, 13.5 Hz, 1H), 2.97 (dd, J=9.2, 13.5 Hz, 1H), 2.77 (dd, J=7.6, 14.2 Hz, 1H), 2.60 (dd, J=7.6, 14.5 Hz, 1H), 1.61-1.48 (m, 1H), 1.42 (d, J=6.9 Hz, 3H), 0.67 (d, J=6.6 Hz, 3H), 0.57 (d, J=6.6 Hz, 3H).

Compounds shown in Working Examples 2 to 7, 15 to 31 were produced in the same manner as in Working Example 1. The physical values of the compounds are presented in Table 1, Table 2, Table 3, and Table 4 below.

(Working Example 8) 3-[4-[(3,5-dichloropyridine-4-carbonyl)amino]phenyl]-2(S)-[3-isobutyl-3-[1(S)-phenylethyl] thioureido] propionate



(Step 1) Thiocarbonyldiimidazole (52 mg, 0.29 mmol) was added to a tetrahydrofuran solution (1.5 ml) of 4-[(3,5-dichloropyridine-4-carbonyl) amino]-L-phenylalanine methyl ester (98 mg, 0.27 mmol) and stirred for 2 hours at room temperature, followed by the addition of a tetrahydrofuran solution (0.5 ml) of N-isobutyl-1 (S)-phenylethyl amine (57 mg, 0.32 mmol) and stirring for 48 hours. The reaction was followed by concentration of the solvent under vacuum and refining of the residue by silica gel column chromatography (n-hexane:ethyl acetate volume ratio = 3:1 6 2:1) to yield pale yellow oily material of 3-[4-[(3,5-dichloropyridine-4-carbonyl)amino]phenyl]-2(S)-[3-isobutyl-3-[1(S)-phenylethyl] thioureido] propionic acid methyl ester (145 mg, 93%). The physical values are presented below.

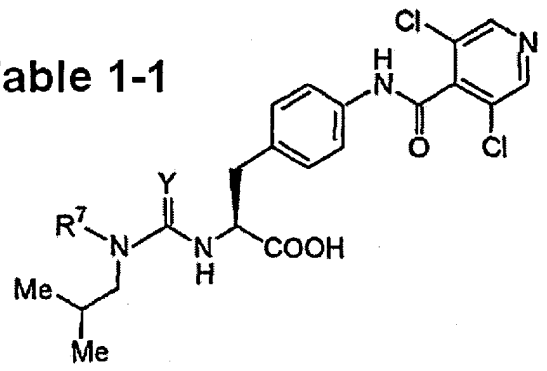
^{1}H-NMR($CDCl_3$) δ: 8.47 (s, 2H), 8.33 (s, 1H), 7.47 (d, J=8.3 Hz, 2H), 7.37-7.28 (m, 5H), 6.99 (d, J=8.3 Hz, 2H), 6.66-6.38 (m, 1H), 5.93 (d, J=6.9 Hz, 1H), 5.51-5.45 (m, 1H), 3.75 (s, 3H), 3.38 (dd, J=6.3, 14.2 Hz, 1H), 3.16 (dd, J=4.6, 14.2 Hz, 1H), 3.12-2.84 (m, 2H), 1.83-1.78 (m, 1H), 1.59 (d, J=7.3 Hz, 3H), 0.80 (d, J=6.6 Hz, 3H), 0.64 (d, J=6.6 Hz, 3H).

(Step 2) The 3-[4-[(3,5-dichloropyridine-4-carbonyl)amino]phenyl]-2(S)-[3-isobutyl-3-[1(S)-phenylethyl] thioureido] propionic acid methyl ester (145 mg, 0.25 mmol) derived in step 1 was dissolved in methanol (4 ml), followed by the addition of 2 mol/liter of lithium hydroxide solution 0.62 ml, 1.23 mmol) and stirring for 2 hours at room temperature. The reaction was followed by the addition of 2 mol/liter of hydrochloric acid at 0^0C to adjust the pH to 3, followed by concentration of the solvent under vacuum. Water was added to the residue followed by filtration to yield pale yellow powder of the title compound (111 mg, 78%). The physical values are presented below.

^{1}H-NMR(DMSO-d_6) δ: 12.71 (brs, 1H), 10.84 (s, 1H), 8.78 (s, 2H), 7.55 (d, J=8.3 Hz, 2H), 7.35-7.20 (m, 7H), 7.00 (d, J=7.9 Hz, 1H), 6.70-6.53 (1, 1H), 5.44-5.36 (m, 1H), 3.24 (dd, J=5.0, 13.9 Hz, 1H), 3.12 (dd. J=8.9, 13.9 Hz, 1H), 3.01 (dd, J=7.9, 14.9 Hz, 1H), 2.85 (dd, J=7.6, 14.9 Hz, 1H), 1.75-1.67 (m, 1H), 1.45 (d, J=6.9 Hz, 3H), 0.64 (d, J=6.6 Hz, 3H). 0.40 (d, J=6.6 Hz, 3H).

Compounds shown in Working Examples 9 to 14, 32 to 39 were produced in the same manner as in Working Example 8. The physical values of the compounds are presented in Table 1, Table 2, and Table 5 below.

Table 1-1



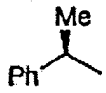
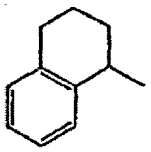
Working Example	Y	R^7	^{1}H-NMR (DMSO-d_6) δ (ppm):
2	O		12.46(brs, 1H), 10.84(s, 1H), 8.79(s, 2H), 7.55(d, J=8.2Hz, 2H), 7.25-7.15(m, 5H), 7.11(d, J=7.3Hz, 2H), 6.31(d, J=7.9Hz, 1H), 5.28(q, J=6.9Hz, 1H), 4.38-4.30(m, 1H), 3.08(dd, J=4.6, 13.5Hz, 1H), 2.98-2.82(m, 2H), 2.42(dd, J=8.3, 14.5Hz, 1H), 1.64-1.51(m, 1H), 1.43(d, J=6.9Hz, 3H), 0.68(d, J=6.6Hz, 3H), 0.61(d, J=6.6Hz, 3H).
3	O		12.49(brs, 1H), 10.84 and 10.83(s, 1H), 8.79(s, 2H), 7.57-7.51(m, 2H), 7.23-6.79(m, 6H), 6.30-6.10 and 6.10-5.90(m, 1H), 5.20-5.00(m, 1H), 4.49-4.36(m, 1H), 3.17-2.23(m, 6H), 1.90-1.73(m, 5H), 0.79-0.71(m, 6H).
4	O	i-Bu	12.40(brs, 1H), 10.80(s, 1H), 8.78(s, 2H), 7.52(d, J=8.3Hz, 2H), 7.22(d, J=8.3Hz, 2H), 6.05(d, J=7.9Hz, 1H), 4.31-4.22(m, 1H), 3.09-2.91(m, 4H), 2.83(dd, J=7.6, 14.2Hz, 2H), 1.78-1.68(m, 2H), 0.73(d, J=6.6Hz, 6H), 0.72(d, J=6.6Hz, 6H).
5	O	Ph	12.61(brs, 1H), 10.84(s, 1H), 8.79(s, 2H), 7.51(d, J=8.3Hz, 2H), 7.38(t, J=7.6Hz, 2H), 7.27(t, J=7.6Hz, 1H), 7.14(d, J=7.6Hz, 2H), 7.05(d, J=8.3Hz, 2H), 5.15(d, J=7.9Hz, 1H), 4.41-4.33(m, 1H), 3.43-3.40(m, 2H), 2.99(dd, J=5.0, 13.5Hz, 1H), 2.90(dd, J=7.6, 13.5Hz, 1H), 1.60-1.50(m, 1H), 0.78(d, J=6.6Hz, 3H), 0.77(d, J=6.6Hz, 3H).

Table 1-2

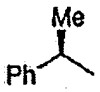
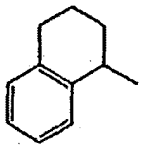
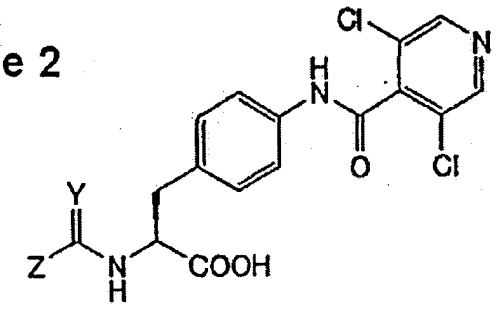
9	S		12.65(brs, 1H), 10.83(s, 1H), 8.78(s, 2H), 7.55(d, J=8.3Hz, 2H), 7.33-7.18(m, 8H), 6.66-6.45(m, 1H), 5.27-5.16(m, 1H), 3.25-3.12(m, 4H), 1.65-1.50(m, 1H), 1.44(d, J=7.3Hz, 3H), 0.54(d, J=6.6Hz, 3H), 0.50(d, J=6.6Hz, 3H).
10	S		12.72(brs, 1H), 10.86 and 10.83(s, 1H), 8.79 and 8.78(s, 2H), 7.59-7.53(m, 2H), 7.26-6.86(m, 7H), 6.75-6.55 and 6.55-6.25(m, 1H), 5.62-5.40 and 5.30-5.13(m, 1H), 3.58-2.28(m, 6H), 2.22-1.55(m, 5H), 0.95-0.48(m, 6H).
11	S	i-Bu	12.55(brs, 1H), 10.81(s, 1H), 8.77(s, 2H), 7.54(d, J=8.2Hz, 2H), 7.24(d, J=8.2Hz, 2H), 7.00(d, J=7.9Hz, 1H), 5.20-5.18(m, 1H), 3.64(dd, J=6.9, 13.9Hz, 2H), 3.23-3.04(m, 4H), 1.91-1.86(m, 2H), 0.75(d, J=6.3Hz, 6H), 0.73(d, J=6.3Hz, 6H).
12	S	Ph	12.84(brs, 1H), 10.84(s, 1H), 8.79(s, 2H), 7.49(d, J=8.3Hz, 2H), 7.44-7.34(m, 3H), 7.14(d, J=7.3Hz, 2H), 6.96(d, J=8.3Hz, 2H), 5.95(d, J=7.6Hz, 1H), 5.10(td, J=5.6, 7.6Hz, 1H), 4.04-3.96(m, 2H), 3.17(dd, J=5.6, 13.7Hz, 1H), 3.00(dd, J=5.6, 13.7Hz, 1H), 1.75-1.65(m, 1H), 0.85(d, J=6.6Hz, 3H), 0.84(d, J=6.6Hz, 3H).

Table 2



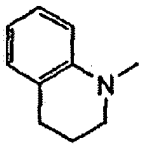
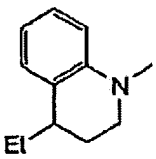
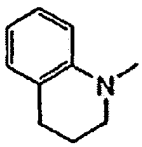
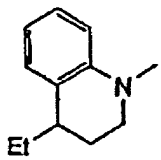
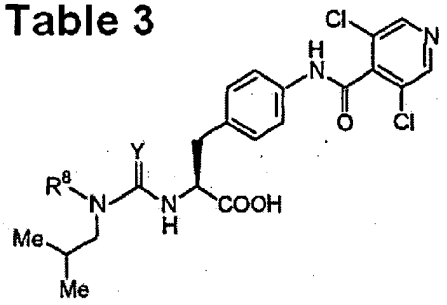
Working Example	Y	Z	^{1}H-NMR (DMSO-d_6) δ (ppm):
6	O		12.59(brs, 1H), 10.86(s, 1H), 8.78(s, 2H), 7.56(d, J=8.3Hz, 2H), 7.23(d, J=8.3Hz, 2H), 7.13(d, J=7.6Hz, 1H), 7.08(d, J=7.6Hz, 1H), 7.01(t, J=7.6Hz, 1H), 6.91(t, J=7.6Hz, 1H), 6.61(d, J=7.9Hz, 1H), 4.40-4.32(m, 1H), 3.64-3.55(m, 1H), 3.51-3.42(m, 1H), 3.08(dd, J=5.3, 13.5Hz, 1H), 2.97(dd, J=9.2, 13.5Hz, 1H), 2.66-2.63(m, 2H), 1.80-1.71(m, 2H).
7	O		12.59(brs, 1H), 10.84(s, 1H), 8.78(s, 2H), 7.58-7.52(m, 2H), 7.25-6.91(m, 6H), 6.57-6.51(m, 1H), 4.42-4.28(m, 1H), 3.72-3.36(m, 2H), 3.16-2.93(m, 2H), 2.64-2.57(m, 1H), 1.88-1.32(m, 4H), 0.90 and 0.86(t, J=7.3Hz, 3H).
13	S		12.83(brs, 1H), 10.87(s, 1H), 8.77(s, 2H), 7.57(d, J=8.3Hz, 2H), 7.50(d, J=7.6Hz, 1H), 7.23-6.99(m, 5H), 6.86(d, J=7.6Hz, 1H), 5.18-5.10(m, 1H), 4.23-4.14(m, 1H), 3.94-3.85(m, 1H), 3.22(dd, J=5.6, 13.9Hz, 1H), 3.09(dd, J=7.6, 13.9Hz, 1H), 2.76-2.67(m, 2H), 1.91-1.83(m, 2H).
14	S		12.89(brs, 1H), 10.90 and 10.86(s, 1H), 8.79(s, 2H), 7.59 and 7.50(d, J=8.3Hz, 2H), 7.40-6.83(m, 6H), 5.22-5.11(m, 1H), 4.43-4.34(m, 1H), 3.76-3.01(m, 4H), 2.73-2.63(m, 1H), 2.05-1.33(m, 4H), 0.88 and 0.85(t, J=7.6Hz, 3H).

Table 3



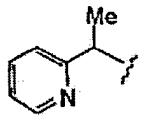
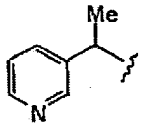
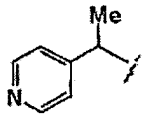
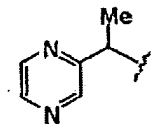
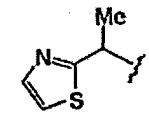
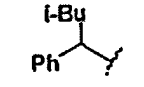
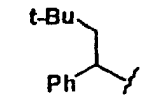
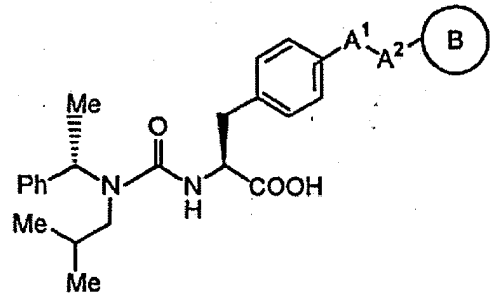
Working Example	Y	R^8	^{1}H-NMR δ (ppm):
15	O		(DMSO-d_6) 0.54-0.70 (6H, m), 1.47 (3H, d, J=7.3 Hz), 1.59 (1H, m), 2.56-3.09 (4H, m) ,4.37 (1H, m), 5.19 (1H, m), 6.53-6.68 (1H, m), 7.02-7.26 (4H, m), 7.52-7.74 (3H, m), 8.46 (1H, d, J=4.3 Hz), 8.80 (2H, s), 10.86 (1H, s), 12.47 (1H, brs).
16	O		(DMSO-d_6) 0.54-0.70 (6H, m), 1.44-1.59 (4H, m), 2.57-3.10 (4H, m), 4.34 (1H, m), 5.29 (1H, m), 6.31 (1H, m), 7.21-7.56 (6H, m), 8.42 (2H, m), 8.80 (2H, s), 10.86 (1H, s), 12.33 (1H, brs).
17	O		(DMSO-d_6) 0.67-0.73 (6H, m), 1.43-1.48 (3H, m), 1.66 (1H, m), 2.60-3.12 (4H, m), 4.42 (1H, m), 5.18 (1H, m), 6.30 (1H, m), 7.02-7.11 (2H, m), 7.25 (2H, d, J=7.3 Hz), 7.54-7.59 (2H, m), 8.40-8.46 (2H, m), 8.80 (2H, s), 10.89 (1H, s), 12.53 (1H, brs).
18	O		(DMSO-d_6) 0.55-0.72 (6H, m), 1.49 (3H, d, J=6.9 Hz), 1.55 (1H, m), 2.71-3.09 (4H, m), 4.28 (1H, m), 5.20 (1H, m), 6.38 (1H, m), 7.19-7.23 (2H, m), 7.53 (2H, d, J=8.2 Hz), 8.46-8.57 (3H, m), 8.80 (2H, s), 10.85 (1H, s), 12.43 (1H, brs).
19	O		(DMSO-d_6) 0.63-0.72 (6H, m), 1.52-1.65 (4H, m), 2.70-3.12 (4H, m), 4.33 (1H, m), 5.39 (1H, q, J=6.9 Hz), 6.36 (1H, m), 7.20-7.24 (2H, m), 7.52-7.68 (4H, m), 8.80 (2H, s), 10.85 (1H, s), 12.46 (1H, brs).
20	O		($CDCl_3$) 0.47-0.51 (3H, m), 0.71 (3H, d, J=6.6 Hz), 0.95 (6H, m), 1.42-1.59 (2H, m), 1.68-1.89 (2H, m), 2.64-2.78 (2H, m), 3.11 (1H, m), 3.25 (1H, m), 4.70 (1H, m), 5.41 (1H, m), 7.11-7.19 (2H, m), 7.29-7.38 (7H, m), 7.54-7.61 (2H, m), 8.55 (2H, s).
21	O		($CDCl_3$) 0.35 (3H, d, J=5.9 Hz), 0.66-0.73 (3H, m), 0.88 (9H, s), 1.43 (1H, m), 1.76 (1H, m), 2.05 (1H, m), 2.77 (2H, m), 3.15 (2H, m), 4.70 (1H, d, J=1.3 Hz), 5.46 (1H, d, J=6.9 Hz), 7.14 (2H, d, J=8.3 Hz), 7.22-7.39 (7H, m), 7.54 (2H, d, J=8.3 Hz), 8.52 (2H, s).

Table 4-1



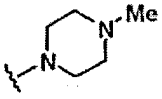
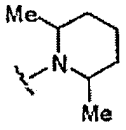
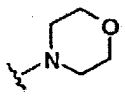
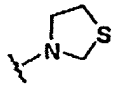
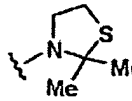
Working Example	A^1	A^2	B	^{1}H-NMR (DMSO-d_6) δ (ppm):
22	O	C=O	 (Na salt)	0.35-0.41 (3H, m), 0.63 (3H, d, J=6.6 Hz), 1.45 (3H, d, J=6.9 Hz), 1.72 (1H, m), 2.20 (3H, s), 2.33 (4H, m), 2.69-3.62 (8H, m), 4.45 (1H, m), 6.85-7.39 (11H, m).
23	O	C=O		0.55 (3H, d, J=6.6 Hz), 0.66 (3H, d, J=6.6 Hz), 1.25 (6H, d, J=6.9 Hz), 1.40 (3H, d, J=6.9 Hz), 1.47-1.99 (7H, m), 2.62 (1H, dd, J=7.6, 14.9 Hz), 2.75 (1H, dd, J=7.3, 14.9 Hz), 2.97 (1H, dd, J=9.3, 13.9 Hz), 3.07 (1H, dd, J=5.0, 13.9 Hz), 4.29-4.40 (2H, m), 5.31 (1H, q, J=6.9 Hz), 6.21 (1H, d, J=7.9 Hz), 6.98 (2H, d, J=8.6 Hz), 7.18-7.32 (7H, m), 12.50 (1H, brs).
24	O	C=O		0.54 (3H, d, J=6.6 Hz), 0.65 (3H, d, J=6.6 Hz), 1.40 (3H, d, J=6.9 Hz), 1.52 (1H, m), 2.64 (1H, dd, J=7.9, 14.5 Hz), 2.75 (1H, dd, J=7.6, 14.5 Hz), 3.00 (1H, dd, J=9.6, 13.9 Hz), 3.07 (1H, dd, J=5.3, 13.9 Hz), 3.41-3.66 (8H, m), 4.37 (1H, m), 5.30 (1H, q, J=6.9 Hz), 6.23 (1H, d, J=7.9 Hz), 7.01 (2H, d, J=8.3 Hz), 7.19-7.33 (7H, m), 12.54 (1H, brs).
25	O	C=O		0.54 (3H, d, J=6.6 Hz), 0.65 (3H, d, J=6.6 Hz), 1.40 (3H, d, J=6.9 Hz), 1.52 (1H, m), 2.64 (1H, dd, J=7.6, 14.5 Hz), 2.75 (1H, dd, J=7.6, 14.5 Hz), 2.94-3.17 (2H, m), 3.68-3.80 (2H, m), 4.32-4.61 (3H, m), 5.30 (1H, q, J=6.9 Hz), 6.23 (1H, d, J=7.9 Hz), 7.03 (2H, d, J=8.0 Hz), 7.20-7.33 (7H, m), 12.52 (1H, brs).
26	O	C=O		0.54 (3H, d, J=6.6 Hz), 0.66 (3H, d, J=6.6 Hz), 1.40 (3H, d, J=6.9 Hz), 1.52 (1H, m), 1.76 (6H, s), 2.62 (1H, dd, J=7.6, 14.5 Hz), 2.75 (1H, dd, J=7.6, 14.5 Hz), 2.93-3.10 (4H, m), 3.97 (2H, m), 4.37 (1H, m), 5.30 (1H, q, J=6.9 Hz), 6.23 (1H, d, J=7.9 Hz), 7.01 (2H, d, J=8.6 Hz), 7.20-7.33 (7H, m), 12.52 (1H, brs).

Table 4-2

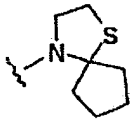
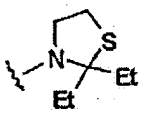
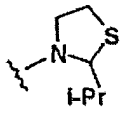
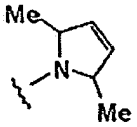
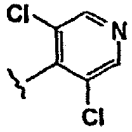
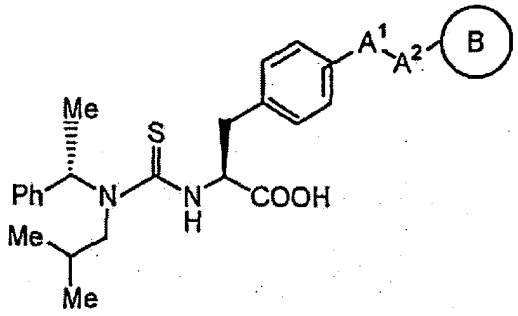
27	O	C=O		0.54 (3H, d, J=6.6 Hz), 0.65 (3H, d, J=6.6 Hz), 1.40 (3H, d, J=6.9 Hz), 1.47-1.84 (6H, m), 2.54 (2H, m), 2.62 (1H, dd, J=7.9, 14.9 Hz), 2.75 (1H, dd, J=6.9, 14.9 Hz), 2.97-3.10 (4H, m), 3.93 (2H, t, J=5.9 Hz), 4.38 (1H, m), 5.30 (1H, q, J=6.9 Hz), 6.23 (1H, d, J=7.9 Hz), 7.02 (2H, d, J=8.6 Hz), 7.06-7.33 (7H, m), 12.53 (1H, brs).
28	O	C=O		0.55 (3H, d, J=6.6 Hz), 0.66 (3H, d, J=6.6 Hz), 0.96 (6H, m), 1.40 (3H, d, J=6.9 Hz), 1.53 (1H, m), 1.73-1.82 (2H, m), 2.14-2.27 (2H, m), 2.61 (1H, dd, J=7.3, 14.9 Hz), 2.75 (1H, dd, J=7.3, 14.9 Hz), 2.93-3.11 (4H, m), 4.00 (2H, m), 4.41 (1H, m), 5.30 (1H, q, J=6.9 Hz), 6.23 (1H, d, J=8.3 Hz), 6.98 (2H, d, J=8.6 Hz), 7.21-7.32 (7H, m), 12.53 (1H, brs).
29	O	C=O		0.54 (3H, d, J=6.6 Hz), 0.65 (3H, d, J=6.6 Hz), 0.94 (6H, d, J=6.3 Hz), 1.40 (3H, d, J=7.3 Hz), 1.52 (1H, m), 2.09 (1H, m), 2.62 (1H, dd, J=7.6, 14.5 Hz), 2.75 (1H, dd, J=7.6, 14.5 Hz), 2.93-3.06 (4H, m), 3.60 (1H, m), 4.17 (1H, m), 4.38 (1H, m), 4.99 (1H, m), 5.30 (1H, q, J=7.3 Hz), 6.23 (1H, d, J=8.3 Hz), 7.03 (2H, d, J=8.3 Hz), 7.21-7.32 (7H, m), 12.53 (1H, brs).
30	O	C=O		0.55 (3H, d, J=6.6 Hz), 0.66 (3H, d, J=6.6 Hz), 1.26-1.42 (9H, m), 1.54 (1H, m), 2.62 (1H, dd, J=7.6, 14.5 Hz), 2.75 (1H, dd, J=7.3, 14.5 Hz), 2.98 (1H, dd, J=9.9, 13.5 Hz), 3.08 (1H, dd, J=4.6, 13.5 Hz), 4.36 (1H, m), 4.51-4.72 (2H, m), 5.31 (1H, q, J=6.9 Hz), 5.79-5.84 (2H, m), 6.20 (1H, d, J=7.9 Hz), 6.99-7.33 (9H, m), 12.50 (1H, brs).
31	O	CH_2		0.53 (3H, d, J=6.6 Hz), 0.65 (3H, d, J=6.6 Hz), 1.40 (3H, d, J=6.9 Hz), 1.52 (1H, m), 2.62 (1H, dd, J=7.6, 14.5 Hz), 2.74 (1H, dd, J=6.9, 14.5 Hz), 2.93 (1H, dd, J=9.6, 13.9 Hz), 3.01 (1H, dd, J=5.0, 13.9 Hz), 4.35 (1H, m), 5.19 (2H, s), 5.30 (1H, q, J=6.9 Hz), 6.13 (1H, d, J=7.6 Hz), 6.94 (2H, J=8.6 Hz), 7.14-7.32 (7H, m), 8.73 (2H, s), 12.48 (1H, brs).

Table 5-1



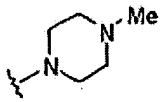
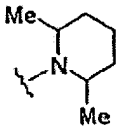
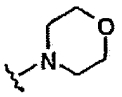
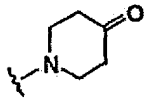
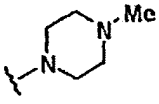
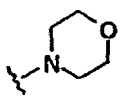
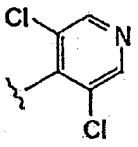
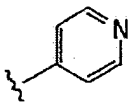
Working example	A^1	A^2	B	^{1}H-NMR (DMSO-d_6) δ (ppm):
32	O	C=O	 (Na salt)	0.35-0.41 (3H, m), 0.63 (3H, d, J=6.6 Hz), 1.45 (3H, d, J=6.9 Hz), 1.72 (1H, m), 2.20 (3H, s), 2.33 (4H, m), 2.69-3.62 (8H, m), 4.45 (1H, m), 6.85-7.39 (11H, m).
33	O	C=O		0.37-0.64 (6H, m), 1.24 (6H, d, J=6.9 Hz), 1.44 (3H, d, J=7.3 Hz), 1.59-1.80 (7H, m), 2.86 (1H, dd, J=7.9, 15.2 Hz), 2.97 (1H, dd, J=7.3, 15.2 Hz), 3.09-3.29 (2H, m), 4.28 (2H, m), 5.27 (1H, m), 6.63 (1H, m), 6.95-7.35 (9H, m), 12.80 (1H, brs).
34	O	C=O		0.34-0.63 (6H, m), 1.44 (3H, d, J=7.3 Hz), 1.70 (1H, m), 2.90 (1H, dd, J=7.9, 15.5 Hz), 3.00 (1H, dd, J=7.9, 15.5 Hz), 3.13 (1H, dd, J=9.5, 14.5 Hz), 3.22 (1H, dd, J=5.9, 15.5 Hz), 3.41-3.65 (8H, m), 5.35 (1H, m), 6.60 (1H, m), 6.99-7.36 (9H, m), 12.74 (1H, brs).
35	O	C=O		0.35-0.63 (6H, m), 1.44 (3H, d, J=7.3 Hz), 1.72 (1H, m), 2.50 (4H, m), 2.90 (1H, m), 3.00 (1H, dd, J=7.9, 15.2 Hz), 3.10-3.26 (2H, m), 3.72-3.85 (4H, m), 5.36 (1H, m), 6.61 (1H, m), 7.05 (2H, d, J=8.3 Hz), 7.21-7.35 (7H, m), 12.75 (1H, brs).
36	NH	C=O	 (Na salt)	0.47 (3H, d, J=6.6 Hz), 0.65 (3H, d, J=6.6 Hz), 1.47 (3H, d, J=6.6 Hz), 1.81 (1H, m), 2.18 (2H, s), 2.28 (4H, m), 2.72-3.50 (8H, m), 4.62 (1H, m), 6.82 (1H, m), 6.95-7.41 (10H, m), 8.51 (1H, s).
37	NH	C=O		0.37-0.65 (6H, m), 1.44 (3H, d, J=6.9 Hz), 1.75 (1H, m), 2.87 (1H, dd, J=8.2, 14.8 Hz), 2.97 (1H, dd, J=7.9, 14.8 Hz), 3.06 (1H, dd, J=8.3, 13.9 Hz), 3.18 (1H, dd, J=5.0, 13.5 Hz), 3.38-3.41 (4H, m), 3.57-3.61 (4H, m), 5.22 (1H, m), 6.65 (1H, m), 6.91-7.47 (9H, m), 8.45 (1H, s), 12.74 (1H, brs).

Table 5-2

38	O	CH_2		0.32 (3H, d, J=6.6 Hz), 0.60 (3H, d, J=6.6 Hz), 1.43 (3H, d, J=6.9 Hz), 1.66 (1H, m), 2.90-3.25 (4H, m), 5.18 (2H, s), 5.24 (1H, m), 6.62 (1H, m), 6.92-7.36 (9H, m), 8.72 (2H, s), 12.56 (1H, brs).
39	O	CH_2		0.32 (3H, d, J=6.6 Hz), 0.58 (3H, d, J=6.9 Hz), 1.43 (3H, d, J=7.6 Hz), 1.67 (1H, m), 2.51-3.24 (4H, m), 5.14 (2H, s), 5.28 (1H, m), 6.59 (1H, m), 6.89 (2H, d, J=8.6 Hz), 7.11-7.41 (11H, m), 8.55 (2H, m), 12.60 (1H, brs).

[Trial Example] VLA-4/VCAM-1 adhesion inhibition trial

The inhibitory activity of the compound pursuant to the present invention on adhesion between Chinese hamster ovarian cells (CHO cells) transfected with human VCAM-1 genes and the promyelocyte-like cell strain HL-60 cells that express VLA-4 was evaluated by the following method.

Aforementioned CHO cells that express VCAM-1 were added to a 96 hole culture plate at the rate of 7×10^3 cells per hole. These were cultured for 3 days in Ham=s F-12 culture medium containing 10 wt% fetal calf serum (FCS) until a confluent state was reached.

HL-60 cells were resuspended in Hanks= solution containing 0.4 wt% bovine serum albumin (BSA) and labeled by the addition of 5 μm of 2',7'-bis (carboxyethyl)-5(6)-carboxyfluorescein penta acetoxymethyl ester (BCECF-AM). Various concentrations of trial substance solution were added to 180 μL of a suspension of 4×10^6/ml of resuspended BCECF labeled HL-60 cells in RPM 11640 culture medium lacking FCS at 20 μL increments, followed by pretreatment for 15 minutes at 37°C. The pretreated HL-60 cells were stratified at the rate of 2×10^5 per hole in a 96 hole culture plate in which VCAM-1 expressed CHO cells had been cultured, followed by adhesion for 5 minutes at 37°C. Subsequently, the plate was filled with 0.4 wt% of BSA Hanks= solution, covered with a sealer and inverted. It was then cultured for an additional 15 minutes. Washing was followed by the addition of PBS containing 1 wt% NP-40 to destroy the cells. The fluorescent intensity of the resulting supernatant was measured by a cyto Fluor 2300 fluorescence measurement system (product of Millipore).

The fluorescent intensity of PBS containing 1% NP-40 was measured as a blank, and the fluorescent intensity of a supernatant derived by adding fluorescent labeled HL-60 suspension to PBS with a 1 wt% NP-40 content in order to destroy the cells so as to reach levels of 2×10^5, 2×10^4, 10^4/ml was measured as a standard.

In the trial results, the cell numbers that adhered to CHO cells that express VCAM-1 as a result of the addition of the control and the trial substance were measured based on a calibration curve drafted from the standard measurements, and the inhibition rate of cell adhesion (%) was computed by the following expression.

Cell adhesion inhibition rate (%) = 100 x [1-(number of adhered cells in trial substance added group/number of adhered cells in control group)]

Table 6 presents the 50% inhibition concentration of the compound pursuant to the present invention derived through this trial.

Table 6

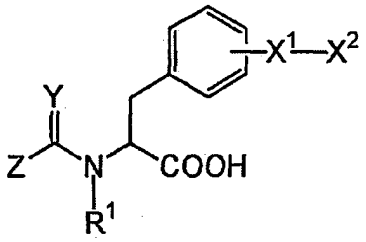
Working Example	50% inhibition concentration (nM)
1	1.1
2	2.7
3	2.1
4	4.7
5	86
6	52
7	20
8	3.7
9	15
10	1.1
11	8.3
12	78
13	89
14	15
15	0.014
16	2.0
17	1.1
18	99
19	2.0
20	0.54
21	3.7
25	47
26	25
34	47

Possibility of Industrial Utilization

The (thio)urea derivatives pursuant to the present invention and their salts exhibit outstanding VLA-4 antagonism and would be useful as therapeutic or prophylactic medicine via VLA-4 for disorders induced by leukocyte adhesion and infiltration or for disorders in which the course of VLA-4 dependent adhesion plays a role.

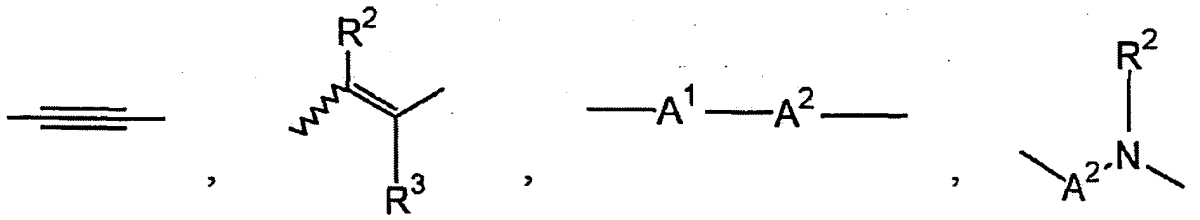
Claims

1. (Thio)urea derivatives or their salts represented by general formula [I]

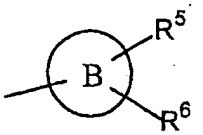


(I)

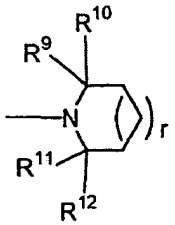
[In the formula, R^1 represents a hydrogen atom, alkyl group, cycloalkyl group, arylalkyl group or heterocyclic alkyl group, X^1 represents a single bond or the following expression



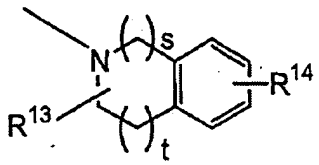
(In the formula, R^2 and R^3 each has the same significance as that of aforementioned R^1, A^1 represents an oxygen atom, sulfur atom, or $-NR^4-$ (In the formula, R^4 has the same significance as R^1), A^2 represents a carbonyl group, thiocarbonyl group, sulfonyl group or $-(CH_2)p-$ (In the formula, p represents an integer of 0 to 5)), X^2 represents the group that is represented by the following expression



(In the formula, B represents a heterocyclic ring, R^5 and R^6 each independently represent a hydrogen atom, a substituent without an organic group, a hydrocarbon group that is directly bound to the carbon atom of a heterocyclic ring or that is bound via an oxygen atom, sulfur atom, oxycarbonyl group, sulfonyl group or sulfinyl group, $-NR^{15}R^{16}$, $-NR^{15}COR^{16}$ or $-NR^{15}SO_2R^{16}$ (In the formula, R^{15} and R^{16} each independently represents a hydrogen atom, hydrocarbon group, hydrocarbyloxy group, heterocyclic group, or heterocyclic alkyl group.), Y represents an oxygen atom or a sulfur atom, Z represents $-NR^7R^8$ (In the formula, R^7 and R8 each independently represents a hydrogen atom, hydrocarbon group, heterocyclic group, heterocyclic alkyl group, $-CR^{17}R^{18}-(CH_2)q-CONR^{19}R^{20}$, $-CR^{17}R^{18}-(CH_2)q-NR^{19}COR^{20}$, $-CR^{17}R^{18}-(CH_2)q-NR^{19}SO_2R^{20}$, $-CR^{17}R^{18}-(CH_2)1-OR^{19}$, $-CR^{17}R^{18}-(CH_2)q-NR^{19}R^{20}$, $-CR^{17}R^{18}-(CH_2)q-SR^{19}$, $-CR^{17}R^{18}-(CH_2)q-SO_2R^{19}$ or $-CR^{17}R^{18}-(CH_2)q-NR^{19}-V-NR^{20}R^{21}$ (In the formula, R^{17} and R^{18} each independently represents a hydrogen atom, alkyl group, cycloalkyl group, hydroxyalkyl group, aminoalkyl group, arylalkyl group or heterocyclic alkyl group, R^{19}, R^{20} and R^{21} each independently has the same significance as R^{15}, V represents a carbonyl group or a thiocarbonyl group, q represents an integer of 0 to 5)), the following expression



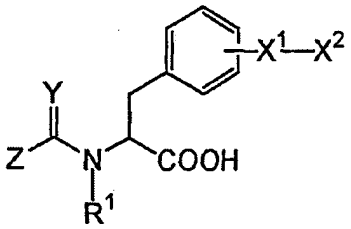
(In the formula, R^9, R^{10}, R^{11}, and R^{12} each independently represents a hydrogen atom, alkyl group having 1 to 6 carbon atoms, r represents an integer of 0 to 3), or the following expression



(In the formula, R^{13} and R^{14} each has the same significance as R^1 s and t each independently represents an integer of 0 to 3).]

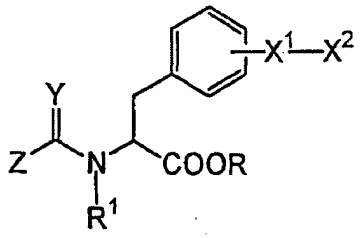
2. The (thio)urea derivatives and their salts of Claim 1 in which R^1 in aforementioned general formula [I] represents hydrogen atoms, alkyl groups having 1 to 6 carbon atoms, cycloalkyl groups having 3 to 7 carbon atoms, arylalkyl groups having 7 to 13 carbon atoms, heterocyclic alkyl groups having 1 to 6 carbon atoms, R^5 and R^6 each independently represent a hydrogen atom, halogen atom, nitro group, cyano group, hydroxyl group, carboxyl group, alkyl groups having 1 to 6 carbon atoms, cycloalkyl groups having 3 to 7 carbon atoms, alkoxy groups having 1 to 6 carbon atoms, aryl groups having 6 to 10 carbon atoms, arylalkyl groups having 7 to 13 carbon atoms, arylalkoxy groups having 7 to 13 carbon atoms, alkoxycarbonyl groups having 2 to 7 carbon atoms, alkylthio groups having 1 to 4 carbon atoms, alkylsulfonyl groups having 1 to 4 carbon atoms, alkylsulfinyl groups having 1 to 4 carbon atoms, $-NR^{15}R^{16}$, $-NR^{15}COR^{16}$ or $-NR^{15}SO_2R^{16}$ (In the formula, R^{15} and R^{16} each independently represent a hydrogen atom, alkyl group having 1 to 6 carbon atoms, alkoxy group having 1 to 6 carbon atoms, cycloalkyl groups having 3 to 7 carbon atoms, aryl groups having 6 to 10 carbon atoms, arylalkyl groups having 7 to 13 carbon atoms, arylalkoxy groups having 7 to 13 carbon atoms, a heterocyclic ring, or heterocyclic alkyl groups having 1 to 6 carbon atoms.), R^7 and R^8 each independently represent a hydrogen atom, alkyl group having 1 to 6 carbon atoms, cycloalkyl group having 3 to 7 carbon atoms, aryl group having 6 to 10 carbon atoms, arylalkyl group having 7 to 13 carbon atoms, heterocyclic group, heterocyclic alkyl group having 1 to 6 carbon atoms, $-CR^{17}R^{18}-(CH_2)q-CONR^{19}R^{20}$, $-CR^{17}R^{18}-(CH_2)q-NR^{19}COR^{20}$, $-CR^{17}R^{18}-(CH_2)q-NR^{19}SO_2R^{20}$, $-CR^{17}R^{18}-(CH_2)q-OR^{19}$, $-CR^{17}R^{18}-(CH_2)q-NR^{19}R^{20}$, $-CR^{17}R^{18}-(CH_2)q-SR^{19}$, $-CR^{17}R^{18}-(CH_2)q-SO_2R^{19}$ or $-CR^{17}R^{18}-(CH_2)q-NR^{19}-V-NR^{20}R^{21}$ (In the formula, R^{17} and R^{18} each independently represent a hydrogen atom, alkyl group having 1 to 6 carbon atoms, a cycloalkyl group having 3 to 7 carbon atoms, a hydroxyalkyl group having 1 to 5 carbon atoms, an aminoalkyl group having 1 to 5 carbon atoms, an arylalkyl group having 7 to 13 carbon atoms and a heterocyclic alkyl group having 1 to 6 carbon atoms, $R^{19}R^{20}$ and R^{21} each independently have the same significance as R^{15}, V represents a carbonyl group or thiocarbonyl group, q represents an integer of 0 to 5).

3. A method of producing the (thio)urea derivatives represented by general formula [I]



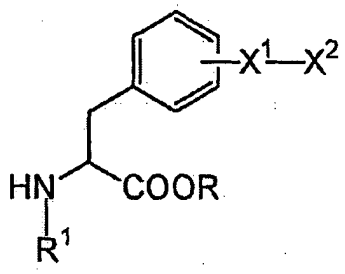
(I)

(In the formula, X^1, X^2, Y, Z and R^1 have the same significance as above)
that is characterized by hydrolysis of any of the compounds represented by general formula [I-a]



(I-a)

(In the formula, X^1, X^2, Y, Z, R^1 and R have the same significance as above)
that are derived by reacting the compound represented by general formula [II]



(II)

(In the formula, X^1, X^2, and R^1 have the same significance as above, R represents an alkyl group having 1 to 6 carbon atoms), Z-H (In the formula, Z has the same significance as above), and a carbonyl group- or thiocarbonyl group-inducted reagent.

4. Medicine containing the (thio)urea derivatives and their salts of Claims 1 or 2 as the active ingredient.

5. VLA-4 antagonist containing the (thio)urea derivatives and their salts of Claims 1 or 2 as the active ingredient.

6. A method of treating disorders involving cell adhesion comprising the administration of the (thio)urea derivatives and their salts of Claims 1 or 2.

7. A method of treating disorders involving cell adhesion comprising the administration of the medicine of Claim 4.

8. A method of treating disorders involving cell adhesion comprising the administration of the VLA-4 antagonist of Claim 5.

9. The method of treatment of Claims 6, 7 and 8 in which cell adhesion via VLA-4 is inhibited.